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SECURITY INFORMATION
CENTRAL INTELLIGENCE AGENCY
INFORMATION FROM
FOREIGN DOCUMENTS OR RADIO BROADCASTS

REPORT

CD NO.

50X1-HUM

COUNTRY GDR

SUBJECT Scientific - Medicine, toxicology

HOW PUBLISHED Monthly periodical

WHERE PUBLISHED Leipzig/Berlin

DATE PUBLISHED Jul 1953

LANGUAGE German

DATE OF INFORMATION 1953

DATE DIST. 25 Sep 1953

NO. OF PAGES 3

SUPPLEMENT TO REPORT NO.

THIS IS UNEVALUATED INFORMATION

SOURCE Chemische Technik, Vol V, No 7, pp 374-75.

DITHIOGLYCERIN, NEW SPECIFICALLY ACTING DRUG FOR TREATMENT OF POISONINGS FROM HEAVY METALS

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/Comment: The newly launched production of 2, 3-dimercaptopropanol on an industrial scale in the GDR is of significance in view of the fact that compounds of this class act as antidotes for poisons of the lewisite class (arsenicals) and various other CW and industrial poisons, including poisons which counteract cholinesterase activity (see A. L. Sinitsina, "Glutathione Metabolism and the Biological Functions of Glutathione," Uspekhi Sovremennoy Biologii, Vol XXXV, No 3, pp 313-337 1953). Also, supposed to counteract the toxic effects of hydrogen cyanide and of some bacterial toxins, i.e., those of diphtheria and tetanus (see A. Mosig, "Dimerceptopropanol Preparations as Detoxicants in Arsenic and Heavy Metal Poisonings," Die Pharmazie, Vol VIII, No 5, pp 403-405, 1953)./

In the search for an antidote to be used in arsenic poisonings, Peters and his collaborators discovered in 1939 the substance 2, 3-dimercaptopropanol, also known as dithioglycerin or BAL /British Anti-Lewisite/. Clinical investigation demonstrated that dithioglycerin is a very effective drug which counteracts damage produced by various toxic metal compounds.

The observation that monothiols are capable of counteracting, to a certain extent, the toxic action of arsenic compounds on bacteria served as a further inducement for investigating the action of thiols as antidotes in metal poisonings. Whereas monothiols such as cysteine or glutathione proved to be rather ineffective, it could be shown that certain proteins, and quite generally those compounds which contain two thiol groups, exhibit a pronounced antidote activity in poisonings due to arsenic compounds, e.g., beta-chlorovinyldichloroarsine. The strong antidote activity of dithiols is due to the fact that a molecule of the arsenic compound

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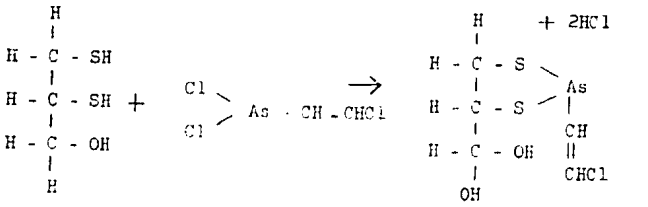
reacts with two thiol groups. The action of the antidotes is much more pronounced when both thiol groups are in the same molecule. It was known that arsenic compounds react with keratoproteins of the skin which contain sulfur and with sulfur-containing enzymes. To reverse these reactions and eliminate the arsenic, an antidote with a superior affinity for arsenic was needed. Such an antidote was found in 2, 3-dimercaptopropanol. This compound counteracts arsenic poisoning in a purely chemical way, as shown by the following equation:



Dimercaptopropanol beta Chlorovinyldichlorarsine /Lewisite/ Detoxification product

The two thiol groups have a great affinity for metals. They remove them from metal-protein complexes formed during poisonings, combine with them, and eliminate them from the body through the kidneys.

It is obvious that dithioglycerin, being a compound has a strong physiological activity, must also exert collateral effects. In addition to the reactions mentioned above, decomposition of metal-protein compounds which are necessary for life also takes place. These comounds include certain respiratory enzymes. Furthermore, the highly active thiol groups activate proteolytic enzymes, e.g., cathepsin. In view of the fact that in addition to metals, halogens also block sulfhydryl groups, sulfhydryl enzymes such as cholinesterase, urease, and pyruvic acid oxidase are inactivated. In this manner, metabolic disturbances are brought about which can be reversed by cysteine or dithioglycerine. All indications are to the effect that intensive and prolonged treatment with dithioglycerin is not compatible with normal metabolism.

The detoxification produced by dithioglycerin is not merely local, but extends to the general phenomena of poisoning if the dithioglycerin has been applied parenterally. In addition to poisonings with arsenic compounds, poisonings with mercury, antimony, silver, copper, cadmium, gold, platinum, bismuth, cobalt, and manganese could be successfully treated. In experimental lead poisoning, increased elimination of lead with the urine could be achieved, but the intermediate lead complex that was formed proved no less toxic than the lead acetate used for poisoning the animals. The action of dithioglycerin in chromium, tellurium, and thallium poisonings has not yet been sufficiently investigated.

The muscle necroses which occasionally arise as a result of the intragluteal injection of dithioglycerin cannot be eliminated as yet. Attempts have been to use a dithioglycerin-glucose compound, which can be administered intravenously, but this compound is not stable when kept for a long time, so that it cannot be manufactured in large quantities. Animal experiments have shown that the success of therapy with dithioglycerin depends on timely application. Dithioglycerin, if applied early enough, combines with heavy metals even after a metal-protein-dithiol complex has already formed.

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After many years of research, the VEB (People-Owned Enterprise) Hydrierwerk Rodleben has launched the production of dithioglycerin in the GDR. The drug is sold under the name Dithioglyzerin Rodlebon. In this manner a drug which had gained international recognition, but was hardly obtainable, has been made generally available.

Dithioglycerin is prepared as follows. After bromine has been added to allyl alcohol, the resulting dibromopropanol is reacted with sodium hydrosulfide to form dithioglycerine, as shown in the following scheme:

$$CH_2 = CH - CH_2OH \xrightarrow{+ Br_2} \underset{Br \quad Br}{CH_2 - CH - CH_2.OH} \xrightarrow{+ NaSH}$$

$$\longrightarrow \underset{SH \quad SH}{CH_2 - CH - CH_2.OH} + 2\ Na\ B$$

Chemical and Physical Properties
of Dithioglyzerin Rodleben

Appearance	Oily, colorless. Has a penetrating odor
Solubility	Easily soluble in organic solvents; soluble with difficulty in water
Sulfur content	51.6%
B. p.	91-92° C at 0.9 mm Hg
Density	1.24
Index of refraction n_D^2	1.5714

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